ORIGINAL ARTICLE

Cancer of the Upper Gastrointestinal Tract among Patients with Pernicious Anemia: A Case–Cohort Study

B.-M. Karlson, A. Ekbom, S. Wacholder, J. K. McLaughlin & A. W. Hsing
Dept. of Surgery, University Hospital, Uppsala, and Dept. of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden; Dept. of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and International Epidemiology Institute, Rockville, Maryland; USA

Karlson B-M, Ekbom A, Wacholder S, McLaughlin JK, Hsing AW. Cancer of the upper gastrointestinal tract among patients with pernicious anemia: a case–cohort study. Scand J Gastroenterol 2000; 35:847–851.

Background: An association between pernicious anemia and stomach cancer has been established in several studies. An increased risk of pancreatic and esophageal cancers has also been reported among pernicious anemia patients. The aim of this case–cohort study was to identify additional risk factors for cancer of the esophagus, stomach, and pancreas among patients with pernicious anemia. **Methods:** A population-based cohort of 4586 patients with pernicious anemia was linked to the Swedish Cancer Registry to identify patients who subsequently developed cancers of the esophagus, stomach, or pancreas using a case–cohort design. A subcohort consisting of 4% of the cohort was randomly selected to serve as the comparison group. Information on medical history, smoking habits, and alcohol use was retrieved from medical charts and analyzed for cancer patients and subcohort members. **Results:** We could not identify any risk factors other than pernicious anemia for stomach cancer. For pancreatic and esophageal cancer, younger age at diagnosis of pernicious anemia was associated with an increased risk. A prior gastric resection, smoking and alcohol abuse were more frequent among esophageal cancer cases than in the subcohort. **Conclusions:** We conclude that a causal relationship between pernicious anemia and subsequent development of esophageal or pancreatic cancers still remains unproven. For esophageal cancer, confounding by smoking and alcohol use is the likely explanation of earlier reports of an association. In the case of stomach cancer, both the inflammatory process, secondary to the pernicious anemia, and pernicious anemia *per se* may be factors leading to malignant transformation.

Key words: Esophageal cancer; gastric cancer; pancreatic cancer; pernicious anemia

Britt-Marie Karlson, M.D., Dept. of Surgery, University Hospital, SE-751 85 Uppsala, Sweden (fax: +46 556808)

Starting with clinical reports in the 1940s, pernicious anemia has been linked to an increased risk of stomach cancer (1–4). More recently, an association between pernicious anemia and pancreatic cancer has been suggested (5, 6), although not all studies have reported an association (7). In a population-based cohort study of almost 4600 patients with pernicious anemia in the Uppsala Health Care Region of Sweden, we observed a threefold increased risk for stomach cancer and a twofold increased risk for pancreatic cancer (6). We also found a threefold increased risk for esophageal cancer, an association not previously reported.

Although there is a strong association between pernicious anemia and gastric cancer, since only a small proportion of pernicious anemia patients develop gastric cancer, other factors (or cofactors) must be involved in gastric carcinogenesis among these patients. It is not possible for logistic reasons to extract information for such factors in all members in the original cohort. There are, however, alternatives. Either of the following can be done: three different case–control studies can be conducted with different control groups for the three outcomes, or a case–cohort study can be conducted with one identical control group for the three outcomes (8, 9). In this setting a case–cohort design is the most cost-effective and was therefore chosen. We thus extracted data from medical records of all stomach, pancreas, and esophageal cancer patients and a randomly selected sample from the original cohort (6).

Materials and Methods

The pernicious anemia cohort

A detailed description of the pernicious anemia cohort study has been reported elsewhere (6). Briefly, the Uppsala

Table I. Reasons for exclusion from the pernicious anemia cohort

	Esophagus cancer *n*, (%)	Stomach cancer *n*, (%)	Pancreas cancer *n*, (%)	Subcohort *n*, (%)	Total
Original patient group	14 (100)	75 (100)	25 (100)	174 (100)	287*
No medical records	2 (14)	3 (4)	1 (4)	19 (11)	25
Erroneous diagnosis of pernicious anemia	0	3 (4)	0	11 (6)	14
Prior gastric resection	3 (21)	15 (20)*	1 (4)	9 (5)*	27*
Final patient group	9 (64)	54 (72)	23 (92)	135 (78)	221

* One member of the subcohort was also diagnosed with stomach cancer after a stomach resection, and is counted in both the stomach cancer and subcohort columns.

Health Care Region, with a population of 1.3 million at the end of the study period, is located in central Sweden. From 1965–1983, all inpatient care in the region was recorded in an Inpatient Registry. Each record includes data on place of residence, hospital department, surgical procedures, and discharge diagnoses. All diagnoses were coded according to the seventh revision of the International Classification of Diseases (ICD-7) through 1968 and according to the eighth revision (ICD-8) thereafter (10). The Inpatient Registry is considered essentially complete for hospitalizations (11). We were able to identify 4586 patients (2064 men and 2522 women) with a discharge diagnosis of pernicious anemia (ICD-7 290.1; ICD8 281.0) between 1965 and 1983. Record linkage to the Swedish Cancer Registry and the Swedish National Death Registry was used to ascertain subsequent cancer occurrence and deaths in the pernicious anemia cohort (12–14).

The cases

In the original cohort, we identified 118 patients with stomach cancer, 18 with esophageal cancer, and 35 with pancreatic cancer. Fifty-nine patients whose cancers were diagnosed during the first 12 months following the diagnosis of pernicious anemia were not included in this study because it was necessary to exclude cases with secondary pernicious anemia due to an underlying cancer; that left 114 cancer patients (75 stomach, 14 esophageal, and 25 pancreatic cancers) for analysis.

The subcohort

A 4% random sample ($n = 174$) of pernicious anemia patients from the original cohort was selected as a subcohort for comparison with the cancer cases, after stratification by year of first diagnosis of pernicious anemia in the Inpatient Register.

Exposure data

For these study subjects, medical records from the first discharge with pernicious anemia were abstracted to obtain the following information: age at diagnosis of pernicious anemia, diagnostic method (vitamin B_{12} deficiency, positive pentagastrin or histamine fraction test, or improvement in the reticulocyte or hemoglobin count within 8 weeks after start of treatment), medical history (stomach resection, diabetes, hypothyroidism, or neuropathy prior to pernicious anemia diagnosis), family history of cancer, smoking, and alcohol use.

Statistical methods

Use of a case–cohort design made it possible to analyze three different outcomes, i.e., esophagus, stomach, and pancreatic cancer, using the same comparison group (subcohort) for analysis (8, 9). Relative risks and 95% confidence intervals were calculated assuming a Poisson distribution (15).

Results

We were unable to retrieve 25 charts (9%) for 6 cases and 19 members of the subcohort. For 14 (5%) patients (3 stomach cancer cases and 11 members of the subcohort), the pernicious anemia diagnosis was erroneous (i.e., corrected later and noted in the charts). For 27 (9.4%), pernicious anemia was secondary to a previous stomach resection. These

Table II. Selected characteristics of the cancer patients and the subcohort/comparison group

	Esophageal	Stomach	Pancreatic	Subcohort
Total, *n* (%)	9 (100)	54 (100)	23 (100)	135 (100)
Sex				
Men, *n* (%)	7 (77.8)	29 (53.7)	10 (43.5)	68 (50.4)
Women, *n* (%)	2 (22.2)	25 (46.3)	13 (56.5)	67 (49.6)
Mean age at diagnosis of pernicious anemia (years)	59.1	67.2	64.0	67.0

Table III. Relative risk (RR) and 95% confidence interval (CI) for cancers of the stomach, esophagus, and pancreas among pernicious anemia patients by age, duration, and medical history

	Esophagus	Stomach	Pancreas
Age at diagnosis of pernicious anemia per year (years)	0.95 (0.9–1.0)	1.01 (0.9–1.0)	0.96 (0.9–1.0)
<55	5.5 (0.7–42.7)	1.1 (0.4–3.1)	3.1 (0.7–13.0)
≥55	1.0 (ref)	1.0 (ref)	1.0 (ref)
Time since diagnosis of pernicious anemia (years)			
<10	1.0 (ref)	1.0 (ref)	1.0 (ref)
10–19	7.4 (0.2–270.5)	1.0 (0.5–2.0)	1.2 (0.3–4.5)
20–29	24.4 (0.2–3160)	0.6 (0.2–1.9)	4.3 (0.9–19.7)
>30	4.8 (0.4–54.6)	1.5 (0.3–7.6)	2.2 (0.3–16.0)
Neuropathy at pernicious anemia diagnosis			
Yes	4.3 (0.3–62.3)	0.4 (0.1–1.4)	0.7 (0.1–4.2)
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Autoimmune disorders			
Diabetes or hypothyroidism (ever)			
Yes	4.9 (0.5–45.6)	0.7 (0.2–1.9)	1.2 (0.3–4.4)
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Diabetes, hypothyroidism or neuropathy (ever)			
Yes	3.8 (0.5–28.5)	0.4 (0.2–1.1)	1.3 (0.4–4.3)
No	1.0 (ref)	1.0 (ref)	1.0 (ref)

66 patients were excluded from analysis, leaving 221 patients for final analysis, of whom 9 had cancer of the esophagus, 54 of the stomach, and 23 of the pancreas (Table I). The characteristics of the study subjects are shown in Table II. Cases with esophageal and pancreatic cancer were younger at the time of diagnosis of pernicious anemia compared with the subcohort.

Table III shows relative risks of the three cancer sites associated with age at diagnosis of pernicious anemia and medical history. In an analysis with age at diagnosis of pernicious anemia as a continuous variable, increasing age was associated with an annual 4%–5% reduction in the risk of esophageal and pancreatic cancer, but this was not significant. Age under 55 years at the diagnosis of pernicious anemia was associated with an increased risk, albeit non-significant, for both esophageal (RR = 5.5, 95% CI 0.7–42.7) and pancreatic cancer (RR = 3.1, 95% CI 0.7–13.0). Likewise a duration of more than 10 years of pernicious anemia was associated with an increased risk for both cancer forms. Moreover, there was an increased risk, although non-significant, for esophageal cancer and a non-significant modest rise in risk (RR = 1.3, 95% CI 0.4–4.3) for pancreatic cancer among patients who had another autoimmune disorder such as diabetes, hypothyroidism, or clinical manifestations of neuropathy prior to the diagnosis of pernicious anemia. However, we were unable to identify any cofactors for patients with stomach cancer. Neither age at diagnosis nor duration of pernicious anemia differed between stomach cancer cases and members of the subcohort.

Both smoking and alcohol abuse were infrequently noted, mainly due to the fact that these exposures were not always recorded in the medical records, but in the case of esophageal cancer both exposures were more frequent among cases compared with the subcohort. Two patients (22%) with esophageal cancer were classified as current smokers in the charts compared with only seven (5%) in the subcohort, and two patients (22%) admitted alcohol abuse or excessive alcohol intake compared with only five (4%) in the subcohort.

Discussion

In our previous cohort study of pernicious anemia patients in the Uppsala Health Care Region, an increased risk of cancers of the esophagus, stomach, and pancreas was reported (6). In the present study, the increased risk for stomach cancer is confirmed, but that for pancreatic or esophagus cancer is not.

The limitations of the present study should be noted. Although there were missing records (9%), the frequency of missing records among cases and subcohort members was similar, and hence selection bias should be minimal. The statistical power of the study was low, due to the small numbers of cases, especially for esophageal and pancreatic cancer. This may be a reason for the lack of significant differences between the cases and the subcohort.

Stomach cancer

One concern in the analysis of stomach cancer is the difficulty in separating the patients with genuine autoimmune pernicious anemia from patients with B_{12} deficiency secondary to chronic gastritis. Pernicious anemia is an autoimmune disorder affecting the whole stomach and is associated with other autoimmune diseases such as diabetes and hypothyroidism (16–19). The criteria used to establish the diagnosis of pernicious anemia between 1965 and 1983 were crude and probably led to the inclusion of patients with a B_{12} deficiency secondary to chronic gastritis affecting only the antrum (20). Chronic mucosal inflammation in the antrum of the stomach causes a deficiency of the intrinsic factor. The intrinsic factor, secreted from the mucosa of the antrum, is necessary for the reabsorption of dietary vitamin B_{12}. Since the diagnosis of

pernicious anemia in the cohort was based on B_{12} deficiency and on the response to B_{12} injections, e.g., an increase of hemoglobin and reticulocyte counts, it is impossible to separate patients with autoimmune pernicious anemia from those with B_{12} deficiency due to chronic mucosal inflammation in the antrum of the stomach.

The time span for progression of chronic atrophic gastritis due to gastric parietal-cell antibodies to gastric atrophy and clinical anemia is 20–30 years (21). This condition leads to achlorhydria and intestinal metaplasia, which is a known risk factor for adenocarcinoma. Our findings that neither age at diagnosis, duration of pernicious anemia, nor presence of other autoimmune manifestations are associated with an increased risk of gastric cancer are therefore of particular interest. These findings imply that a patient with autoimmune gastritis does not differ in cancer risk from patients with B_{12} deficiency secondary to chronic gastritis. This could be interpreted to mean that an inflammatory process in the stomach mucosa *per se* is important in the development of stomach cancer, a parallel phenomenon to the increased risk following stomach resection (20, 22).

Pancreatic and esophageal cancer

Different biological mechanisms have been proposed as explanations for a relation between pernicious anemia and pancreatic cancer. Diabetes is known to be associated with pancreatic cancer (23), but cannot be the sole explanation for the increased risk, as only four pancreatic cancer patients with pernicious anemia have had diabetes. The absence of an acidic environment in the stomach may foster the development of carcinogenic compounds that may play a role in malignant transformation of the pancreas. This could be further aggravated by increased serum levels of gastrin also associated with pernicious anemia. Gastrin is known to have a trophic effect on the pancreas and may therefore be a promoter or even an initiator of pancreatic cancer (5, 24). Although there was an association between younger age at onset of pernicious anemia and pancreatic cancer, the presence of autoimmune disorders such as diabetes or hypothyroidism and/or neuropathy was not associated with an increased risk. These findings argue against a strong association between pernicious anemia and pancreatic cancer, in spite of the mechanism that has been proposed. Moreover, a Danish study of pernicious anemia patients found no increase in risk for pancreatic cancer (7). Our validation efforts showed that a prior stomach resection or an erroneous diagnosis of pernicious anemia was as high as 14.4% in the present study. These factors were, however, less frequent among pancreatic cancer cases compared with members of the subcohort. Therefore, the observed excess risk reported from the original cohort study for pancreatic cancer would be somewhat higher if patients with an erroneous diagnosis or a gastric resection were excluded from the original cohort. For esophageal cancer, because a prior gastric resection and a history of excessive alcohol intake and/or smoking were more common among the cases than the subcohort members, the reported excess in esophageal cancer could be a result of confounding by these factors.

In summary, this study did not reveal any specific characteristic in patients with pernicious anemia leading to an increased risk of stomach cancer, and the underlying biological mechanism remains unclear. Our results do not support an association between pernicious anemia and pancreatic cancer. Further follow-up and expansion of the present cohort, along with other studies, however, are needed in order to confirm or rule out such an association.

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Received 31 August 1999
Accepted 28 January 2000